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UNITED STATES PATENT APPLICATION

for

PHARMACEUTICAL DOSAGE FORM CAPABLE OF MAINTAINING STABLE DISSOLUTION PROFILE UPON STORAGE

by

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PHARMACEUTICAL DOSAGE FORM CAPABLE OF MAINTAINING STABLE DISSOLUTION PROFILE UPON STORAGE

[0001] This application is a continuation-in-part of U.S. application Serial No. 10/119,129 filed on 09 April 2002, which claims priority of U.S. provisional application Serial No. 60/284,381 filed on 17 April 2001 and U.S. provisional application Serial No. 60/326,952 filed on 04 October 2001. This application also claims priority of U.S. provisional application Serial No. 60/399,862 filed on 31 July 2002, U.S. provisional application Serial No. 60/399,776 filed on 31 July 2002, U.S. provisional application Serial No. 60/399,863 filed on 31 July 2002, and U.S. provisional application Serial No. 60/399,808 filed on 31 July 2002.

FIELD OF THE INVENTION

[0002] The present invention relates to gelatin capsules filled with a fill material comprising a selective COX-2 inhibitory drug of low water solubility.

BACKGROUND OF THE INVENTION

[0003] Gelatin, a mixture of water-soluble proteins derived from collagen by hydrolysis, is widely used in the pharmaceutical and food industries, among others. One major application of gelatin is in preparation of both hard and soft gelatin capsules. Such capsules are desirable for, *inter alia*, their versatility (they may contain drug formulations in solid, semi-solid, or liquid form) and for their rapid dissolution characteristics. Unfortunately, drug dosage forms containing gelatin in an outer layer (*e.g.* liquid or powder filled into a gelatin capsule) can exhibit a drop in dissolution rate over time. This drop in dissolution rate can lead to undesirable and unacceptable alterations in *in vitro* dissolution profile and in bioavailability, especially for drugs of low water solubility or drugs whose absorption is dissolution-rate limited. Such changes in dissolution profile are thought to result from cross-linking of gelatin occurring in gelatin capsule shells.

[0004] Singh *et al.*, Alteration in Dissolution Characteristics of Gelatin-Containing Formulations, *Pharmaceutical Technology*, April 2002, hereby incorporated by reference herein but not admitted to be prior art, describes reports suggesting that several agents including glycerine, glycine, and hydroxylamine hydrochloride, when incorporated into fill contents of gelatin capsules, can limit gelatin cross-linking. Unfortunately, existing methods directed at the problem of gelatin cross-linking in

capsule shells are less than satisfactory, especially in situations where longer shelf life and stability through real life storage, shipping and handling conditions are desired; pursuit of adequate solutions to the problem of gelatin capsule cross-linking is therefore desired.

[0005] If a pharmaceutical dosage form comprising a fill material in a gelatin capsule could be prepared which dosage form is capable of providing stable drug dissolution rate, even after storage under stressed conditions, a significant advance in the oral delivery of drugs, especially drugs of low water solubility or drugs whose absorption is dissolution-rate limited, would result.

SUMMARY OF THE INVENTION

[0006] There is now provided in the present invention a pharmaceutical dosage form comprising a fill material sealed in a gelatin capsule shell, the fill material comprising (a) a selective COX-2 inhibitory drug of low water solubility, and (b) an amine agent comprising at least one pharmaceutically acceptable primary or secondary amine.

[0007] Desirably, the amine agent in the dosage form is present at a concentration sufficient to inhibit cross-linking of the gelatin and/or pellicle formation in the capsule shell.

[0008] The dosage form of the present invention is especially useful for dosage forms with liquid fill materials and for dosage forms with soft gelatin capsules

[0009] The term "pellicle" herein refers to a relatively water-insoluble membrane formed in a gelatin capsule shell wherein the membrane tends to be thin, tough, and rubbery. It is now understood that one mechanism underlying pellicle formation is gelatin cross-linking. Gelatin cross-linking and pellicle formation result in reduced dissolution rates. Accordingly, quantification of dissolution rate of a first capsule within a reasonably short time after capsule preparation and of a second capsule after storage under stressed conditions (e.g. four weeks at 40°C and 85% relative humidity in a closed container) as described herein provides one means of assessing pellicle formation and/or gelatin cross-linking. The term "within a reasonably short time after capsule formation" means within a period of time such that substantial cross-linking and/or pellicle formation is unlikely to have yet occurred, for example within one week, dependent upon storage condition during that period.

[0010] The term "pellicle resistant" herein means that such a gelatin capsule so

described has a reduced tendency to form, or exhibits slowed, delayed or reduced formation of a pellicle upon storage under stressed conditions. Similarly, "inhibition of cross-linking" (or "inhibition of pellicle formation") herein means a slowed, delayed or reduced formation of gelatin cross-links (or pellicle formation) by comparison with an amount a similar capsule lacking only agent as provided herein.

[0011] Pharmaceutical dosage forms according to the present invention have been found to exhibit an unexpected and surprisingly substantial reduction in cross-linking of gelatin in the capsule shell and pellicle formation. As a result, such dosage forms are capable of consistently meeting desired *in vitro* dissolution criteria, even after storage under stressed conditions. This invention represents a significant improvement over conventional dosage forms and conventional gelatin capsule shells.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] Figure 1 is a graph showing Tier I dissolution rate of Formulation 30 following storage at 25° C as described in Example 3.

[0013] Figure 2 is a graph showing Tier I dissolution rate of Formulation 30 following storage at 40° C as described in Example 3.

[0014] Figure 3 is a graph showing Tier II dissolution rate of Formulation 30 following storage at 25° C as described in Example 3.

[0015] Figure 4 is a graph showing Tier II dissolution rate of Formulation 30 following storage at 40° C as described in Example 3.

[0016] Figure 5 is a graph showing Tier I dissolution rate of Formulation 19 following storage at 25° C as described in Example 3.

[0017] Figure 6 is a graph showing Tier I dissolution rate of Formulation 19 following storage at 40° C as described in Example 3.

[0018] Figure 7 is a graph showing Tier II dissolution rate of Formulation 19 following storage at 40° C as described in Example 3.

DETAILED DESCRIPTION OF THE INVENTION

[0019] In one embodiment, the present invention provides a dosage form comprising a fill material sealed in a gelatin capsule shell, the fill material comprising (a) a selective cyclooxygenase-2 inhibitory drug of low water solubility and (b) an amine agent comprising at least one pharmaceutically acceptable primary or secondary amine

wherein the amine agent is present in an amount sufficient to inhibit cross-linking and/or pellicle formation in the gelatin capsule shells upon storage.

Gelatin cross-linking, pellicle formation, and drug dissolution.

[0020] Without being bound by theory, the inventors' believe that gelatin cross-linking can result from a process by which amino acid residues of gelatin covalently bond to form an insoluble material. The process can be the result of low levels of aldehydes coming into contact with the gelatin. Cross-linking of a gelatin capsule can impact product performance by delaying the release of the formulation (containing the active compound) from the capsule shell. The delay in release can, in turn, affect the rate of absorption of the compound into the blood stream and clinical onset of action. While 'mild' cross-linking does not necessarily have a significant impact on release of the formulation from the dosage form, 'severe' cross-linking can have a significant impact. When cross-linking is severe, it can lead to a delay of release of formulation from the dosage form in humans, potential bioequivalence problems, and a potential delay in clinical onset of action.

[0021] Dosage forms of the present invention exhibit decreased gelatin cross-linking (and pellicle formation) and, therefore, when placed in an *in vitro* dissolution assay, are capable of advantageously exhibiting less dissolution rate change during storage under stressed conditions than conventional dosage forms. Dosage forms according to the present invention also exhibit more uniform inter-dosage form drug dissolution rate than standard dosage forms.

[0022] In one embodiment of the present invention wherein the fill material further comprises at least one substance that promotes cross-linking of gelatin when in contact therewith (the substance being the drug itself or an excipient substance, and the substance acting independently or in combination with one or more other substances to promote said cross-linking); upon (a) immediately testing a first dosage form in a first *in vitro* dissolution assay; (b) storing a second dosage form which is identical to the first dosage form in a closed container maintained at 40 °C and 75% relative humidity for a period of four weeks and, after said storage; (c) testing the second dosage form in a second *in vitro* dissolution assay which is identical to the first *in vitro* dissolution assay; the amount of drug dissolved at 45 minutes in the second dissolution assay is within ± 15 percent and preferably within ± 10 percent of the amount of drug dissolved at 45 minutes

in the first dissolution assay.

[0023] Because gelatin cross-linking may lead to delayed dissolution, storage time-dependent delays in dissolution profile may be a good indicator of gelatin cross-linking during such storage. There are a number of *in vitro* dissolution assays suitable for determining dissolution profile. Indeed, one skilled in the art is able to design additional assays or modifications thereof. Two dissolution-type test methods were developed and set forth herein and designated the "Tier I" and "Tier II "tests.

[0024] In the Tier I test, a dosage form is placed in a USP apparatus II with a rotating paddle with a paddle speed of 50 rpm in 900 mL of 0.01N HCl + 1% Tween 80. Samples are typically withdrawn at 15, 30, 45, 60 and 90 minutes and assayed for drug content by HPLC.

[0025] The Tier II test employs the addition of the enzyme pepsin to the media. Pepsin in the human stomach digests cross-linked gelatin. The appropriate amount of pepsin added to the media (750,000 units/L) was determined and reported in Collaborative Development of Two-Tier Dissolution Testing for Gelatin Capsules and Gelatin-Coated Tablets using Enzyme-Containing Media, Stimuli to the Revision Process, Pharmacopeial Forum, Vol. 25, No. 5, Sept.-Oct. 1998. The Tier II drug release test designed in this way is expected to produce a drug release profile that is a reasonable approximation of the drug release profile in humans.

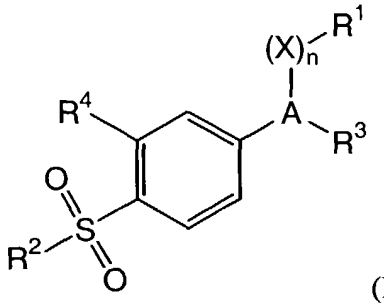
[0026] An 'initial' drug release profile is determined for each dosage form within a reasonably short time after formation (i.e. dosage form before the formulation is exposed to conditions which might result in gelatin cross-linking, such as temperature or relative humidity). A subsequent profile is determined for samples pulled at subsequent time points. A change from initial to subsequent Tier I profile (i.e. a delay in dissolution) is presumptively attributed to gelatin cross-linking. When such a change is reduced in the Tier II assay (containing pepsin), this reduction is deemed further evidence of gelatin cross-linking upon storage.

Fill material

Selective cyclooxygenase-2 inhibitory drug.

[0027] Dosage forms of the invention comprise a selective cyclooxygenase-2 inhibitory drug, also referred to herein as a selective COX-2 inhibitory drug. Preferably,

the COX-2 inhibitory drug is a drug of low water solubility (*e.g.* having a room temperature solubility in water of not more than about 10 mg/ml and more preferably not more than about 1 mg/ml). A preferred selective COX-2 inhibitory drug useful herein, or to which a salt or prodrug useful herein is converted *in vivo*, is a compound of formula (I)



(I)

wherein:

A is a substituent selected from partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings, preferably a heterocyclyl group selected from pyrazolyl, furanonyl, isoxazolyl, pyridinyl, cyclopentenonyl and pyridazinonyl groups;

X is O, S or CH_2;

n is 0 or 1;

R^1 is at least one substituent selected from heterocyclyl, cycloalkyl, cycloalkenyl and aryl, and is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

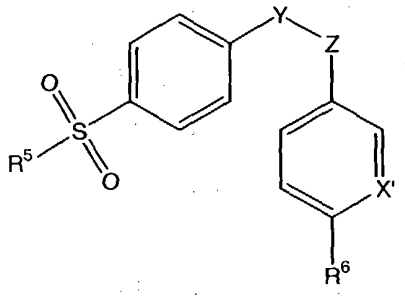
R^2 is methyl, amino or aminocarbonylalkyl;

R^3 is one or more radicals selected from hydrido, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-

aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl and N-alkyl-N-arylaminosulfonyl, R^3 being optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio; and

R^4 is selected from hydrido and halo.

[0028] Dosage forms of the invention are especially useful for selective COX-2 inhibitory drugs having the formula (II):



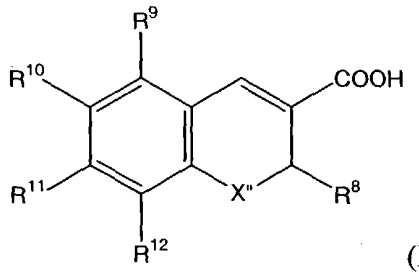
(II)

where R^5 is a methyl or amino group, R^6 is hydrogen or a C_{1-4} alkyl or alkoxy group, X' is N or CR^7 where R^7 is hydrogen or halogen, and Y and Z are independently carbon or nitrogen atoms defining adjacent atoms of a five- to six-membered ring that is optionally substituted at one or more positions with oxo, halo, methyl or halomethyl groups, or an isomer, tautomer, pharmaceutically-acceptable salt or prodrug thereof. Preferred such five- to six-membered rings are cyclopentenone, furanone, methylpyrazole, isoxazole and pyridine rings substituted at no more than one position.

[0029] Illustratively, dosage forms of the invention are suitable for celecoxib, deracoxib, valdecoxib, rofecoxib, etoricoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one, 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3-(2H)-pyridazinone, pharmaceutically acceptable salts and prodrugs thereof. A especially useful prodrug of valdecoxib for use in dosage forms of the invention is parecoxib, preferably parecoxib sodium.

[0030] Dosage forms of the invention are also useful for compounds having the

formula (III):



(III)

where X" is O, S or N-lower alkyl; R^8 is lower haloalkyl; R^9 is hydrogen or halogen; R^{10} is hydrogen, halogen, lower alkyl, lower alkoxy or haloalkoxy, lower aralkylcarbonyl, lower dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, or 5- or 6-membered nitrogen-containing heterocyclosulfonyl; and R^{11} and R^{12} are independently hydrogen, halogen, lower alkyl, lower alkoxy, or aryl; and for pharmaceutically acceptable salts thereof.

[0031] A especially useful compound of formula (III) is (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, especially in the form of a water-soluble salt thereof, for example the sodium salt.

[0032] Where the drug is celecoxib, the dosage form typically comprises celecoxib in a therapeutically and/or prophylactically effective total amount of about 10 mg to about 1000 mg per dose unit. Where the drug is a selective COX-2 inhibitory drug other than celecoxib, the amount of the drug per dose unit is therapeutically equivalent to about 10 mg to about 1000 mg of celecoxib.

[0033] It will be understood that a therapeutically and/or prophylactically effective amount of a drug for a subject is dependent *inter alia* on the body weight of the subject. A "subject" herein to which a therapeutic agent or composition thereof can be administered includes a human patient of either sex and of any age, and also includes any nonhuman animal, especially a domestic or companion animal, illustratively a cat, dog or horse.

[0034] Where the subject is a child or a small animal (*e.g.*, a dog), for example, an amount of celecoxib relatively low in the preferred range of about 10 mg to about 1000 mg is likely to be consistent with therapeutic effectiveness. Where the subject is an adult human or a large animal (*e.g.*, a horse), therapeutic effectiveness is likely to require dose units containing a relatively greater amount of celecoxib. For an adult human, a therapeutically effective amount of celecoxib per dose unit in a dosage form of the present

invention is typically about 10 mg to about 400 mg. Especially preferred amounts of celecoxib per dose unit are about 100 mg to about 200 mg, for example about 100 mg or about 200 mg.

[0035] For other selective COX-2 inhibitory drugs, an amount of the drug per dose unit can be in a range known to be therapeutically effective for such drugs. Preferably, the amount per dose unit is in a range providing therapeutic equivalence to celecoxib in the dose ranges indicated immediately above.

Amine agent in the fill material.

[0036] An amine agent in a dosage form of the invention may be any pharmaceutically acceptable primary or secondary amine compound. The term "primary or secondary amine compound" herein includes those primary and secondary amines which are pharmaceutically acceptable excipients. Preferably, primary or secondary amine compounds of the present invention are compounds that are not therapeutically or nutritionally active. Non-limiting examples of suitable primary amine compounds include tromethamine (also known and referred to herein as "Tris" or tris(hydroxymethyl)aminomethane), ethanolamine, ethylenediamine, diethylamine, ethylene N-methyl-D-glucamine, and amino acids such as L-arginine, L-lysine, and guanidine. Non-limiting examples of suitable secondary amine compounds include diethanolamine, benethamine (*i.e.*, N-phenymethyl)benezeneethanamine), benzathine (*i.e.*, N,N-dibenzylethylenediamine), piperazine, hydrabamine (*i.e.*, N,N-bis(dehydroabietyl)ethylenediamine), and imidazole. Preferably, the primary or secondary amine compound is present in a dosage form of the invention in a total amine agent amount of not more than about 10%, preferably not more than about 7%, and more preferably not more than about 5% of the dosage form on a dry weight basis, for example about 0.1% to about 4%. It should be understood that "on a dry weight basis" means total weight excepting water weight..

[0037] In a first preferred embodiment, about 50%, preferably at least about 55%, more preferably at least about 60%, and still more preferably at least about 65% the total amine agent amount present in a dosage form of the invention is present in the fill material.

Sulfite compound in the fill material.

[0038] The dosage form of the present invention may optionally comprise any pharmaceutically acceptable sulfite compound. Illustrative pharmaceutically acceptable sulfite compounds include sodium metabisulfite, sodium bisulfite, and sodium thiosulfate (sodium hyposulfite). One or more sulfite compounds are optionally present in a composition of the invention in an amount of not more than about 10%, for example about 0.01% to about 5%, and preferably about 0.1% to about 2%, of the dosage form on a dry weight basis. The sulfite compound can alternatively or additionally be present in the gelatin capsule wall.

[0039] In a preferred embodiment, at least about 40%, preferably at least about 50%, still more preferably at least about 55%, even more preferably at least about 60%, and yet more preferably at least about 70% of all sulfite compound present in a dosage form of the invention is present in the fill material.

Other excipients.

[0040] Optionally, a fill material according to the invention can comprise any additional pharmaceutically acceptable excipients. Such excipients can include, by way of illustration and not limitation, diluents, disintegrants, dispersants, binding agents, adhesives, wetting agents, lubricants, glidants, crystallization inhibitors, stabilizers, antioxidants, substances added to mask or counteract a disagreeable taste or odor, flavors, dyes, fragrances, preservatives, and substances added to improve appearance of the dosage form.

[0041] Such optional additional components should be physically and chemically compatible with the other ingredients of the fill material and should not be deleterious to the recipient. Importantly, some of the above-listed classes of excipients overlap each other.

[0042] Fill material of the present invention optionally further comprises at least one pharmaceutically acceptable free radical-scavenging antioxidant. A free radical-scavenging antioxidant is to be contrasted with a "non-free radical-scavenging antioxidant", *i.e.*, an antioxidant that does not possess free radical-scavenging properties. Non-limiting illustrative examples of suitable free radical-scavenging antioxidants include α-tocopherol (vitamin E), ascorbic acid (vitamin C) and salts thereof including sodium ascorbate and ascorbic acid palmitate, butylated hydroxyanisole (BHA), butylated

hydroxytoluene (BHT), fumaric acid and salts thereof, hypophosphorous acid, malic acid, alkyl gallates, for example propyl gallate, octyl gallate and lauryl gallate, sodium sulfite, sodium bisulfite and sodium metabisulfite. Preferred free radical-scavenging antioxidants are alkyl gallates, vitamin E, BHA and BHT. More preferably the at least one free radical-scavenging antioxidant is propyl gallate.

[0043] One or more free radical-scavenging antioxidants are optionally present in dosage forms of the invention in a total amount effective to substantially reduce formation of an addition compound, typically in a total amount of about 0.01% to about 5%, preferably about 0.01% to about 2.5%, and more preferably about 0.01% to about 1%, by weight of the fill material.

[0044] Fill material according to the invention optionally comprises one or more pharmaceutically acceptable sweeteners. Non-limiting examples of suitable sweeteners include mannitol, propylene glycol, sodium saccharin, acesulfame K, neotame and aspartame. Alternatively or in addition, a viscous sweetener such as sorbitol solution, syrup (sucrose solution) or high-fructose corn syrup can be used and, in addition to sweetening effects, can also be useful to increase viscosity and to retard sedimentation.

[0045] Fill material of the invention optionally comprises one or more pharmaceutically acceptable preservatives other than free radical-scavenging antioxidants. Non-limiting examples of suitable preservatives include benzalkonium chloride, benzethonium chloride, benzyl alcohol, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate, thimerosal, *etc.*

[0046] Fill material of the invention optionally comprises one or more pharmaceutically acceptable wetting agents. Surfactants, hydrophilic polymers and certain clays can be useful as wetting agents to aid in dissolution and/or dispersion of a hydrophobic drug such as celecoxib. Non-limiting examples of suitable surfactants include benzalkonium chloride, benzethonium chloride, cetylpyridinium chloride, dioctyl sodium sulfosuccinate, nonoxynol 9, nonoxynol 10, octoxynol 9, poloxamers, polyoxyethylene (8) caprylic/capric mono- and diglycerides (*e.g.*, Labrasol™ of Gattefossé), polyoxyethylene (35) castor oil, polyoxyethylene (20) cetostearyl ether, polyoxyethylene (40) hydrogenated castor oil, polyoxyethylene (10) oleyl ether, polyoxyethylene (40) stearate, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80 (*e.g.*, Tween™ 80 of ICI), propylene glycol laurate (*e.g.*, Lauroglycol™ of Gattefossé),

sodium lauryl sulfate, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, sorbitan monostearate, tyloxapol, and mixtures thereof.

[0047] Additionally, fill material of the invention optionally comprise one or more pharmaceutically acceptable buffering agents, flavoring agents, colorants, stabilizers and/or thickeners. Buffers can be used to control pH of a formulation and can thereby modulate drug solubility. Flavoring agents can enhance patient compliance by making the dosage form more palatable, and colorants can provide a product with a more aesthetic and/or distinctive appearance. Non-limiting examples of suitable colorants include D&C Red No. 33, FD&C Red No. 3, FD&C Red No. 40, D&C Yellow No. 10, and C Yellow No. 6.

Liquid fill material

[0048] In a preferred embodiment, fill material comprising the selective COX-2 inhibitory drug is in the form of a liquid. More preferably, the fill material is self-emulsifying upon contact with simulate gastric fluid.

Solvents

[0049] Fill material according to this embodiment comprises at least one solvent which is preferably suitable for dissolving the drug and/or any additional ingredients or excipients present therein.

i. Glycols and glycol ethers

[0050] A preferred solvent is a glycol or glycol ether. Suitable glycol ethers include those conforming to formula (X):

$$R^1—O—((CH_2)_mO)_n—R^2 \qquad (X)$$

wherein R^1 and R^2 are independently hydrogen or C_{1-6} alkyl, C_{1-6} alkenyl, phenyl or benzyl groups, but no more than one of R^1 and R^2 is hydrogen; m is an integer of 2 to about 5; and n is an integer of 1 to about 20. It is preferred that one of R^1 and R^2 is a C_{1-4} alkyl group and the other is hydrogen or a C_{1-4} alkyl group; more preferably at least one of R^1 and R^2 is a methyl or ethyl group. It is preferred that m is 2. It is preferred that n is an integer of 1 to about 4, more preferably 2.

[0051] Glycol ethers used as solvents in fill material typically have a molecular weight of about 75 to about 1000, preferably about 75 to about 500, and more preferably about 100 to about 300. Importantly, the glycol ethers used in fill material of this

embodiment must be pharmaceutically acceptable and must meet all other conditions prescribed herein.

[0052] Non-limiting examples of glycol ethers that may be used in fill material of this embodiment include ethylene glycol monomethyl ether, ethylene glycol dimethyl ether, ethylene glycol monoethyl ether, ethylene glycol diethyl ether, ethylene glycol monobutyl ether, ethylene glycol dibutyl ether, ethylene glycol monophenyl ether, ethylene glycol monobenzyl ether, ethylene glycol butylphenyl ether, ethylene glycol terpinyl ether, diethylene glycol monomethyl ether, diethylene glycol dimethyl ether, diethylene glycol monoethyl ether, diethylene glycol diethyl ether, diethylene glycol divinyl ether, ethylene glycol monobutyl ether, diethylene glycol dibutyl ether, diethylene glycol monoisobutyl ether, triethylene glycol dimethyl ether, triethylene glycol monoethyl ether, triethylene glycol monobutyl ether, tetraethylene glycol dimethyl ether, and mixtures thereof. See for example Flick (1998): Industrial Solvents Handbook, 5th ed., Noyes Data Corporation, Westwood, NJ. An especially suitable glycol ether solvents are diethylene glycol monoethyl ether, sometimes referred to in the art as DGME or ethoxydiglycol. It is available for example under the trademark Transcutol™ of Gattefossé Corporation.

[0053] Glycols suitable as solvents in fill material include propylene glycol, 1,3-butanediol and polyethylene glycols. A presently preferred solvent is polyethylene glycol (PEG).

[0054] Any pharmaceutically acceptable PEG can be used. Preferably, the PEG has an average molecular weight of about 100 to about 10,000, and more preferably about 100 to about 1,000. Still more preferably, the PEG is of liquid grade. Non-limiting examples of PEGs that can be used in solvent liquids of this invention include PEG-200, PEG-350, PEG-400, PEG-540 and PEG-600. See for example Flick (1998), *op. cit.*, p. 392. A presently preferred PEG has an average molecular weight of about 375 to about 450, as exemplified by PEG-400.

[0055] PEGs such as PEG-400 have many desirable properties as solvents for poorly water-soluble drugs. In the case of celecoxib, for example, the drug can be dissolved or solubilized at a very high concentration in PEG-400, enabling formulation of a therapeutically effective dose in a very small volume of solvent liquid. This is especially important where the resulting solution is to be encapsulated, as capsules of a

size convenient for swallowing can be prepared containing a therapeutically effective dose even of a drug such as celecoxib having a relatively high dose requirement for efficacy. Importantly, ethanol, water, and other excipients identified as co-solvents hereinbelow or elsewhere can, if desired, be used as solvents in a fill material of the invention. Typically, one or more solvents will be present in a fill material in a total amount of about 5% to about 95%, preferably about 10% to about 90% and more preferably about 15% to about 85%, by weight of the fill material.

Co-solvents.

[0056] A fill material of this embodiment optionally comprises one or more pharmaceutically acceptable co-solvents. Non-limiting examples of suitable co-solvents include additional glycols, alcohols, for example ethanol and n-butanol; oleic and linoleic acid triglycerides, for example soybean oil; caprylic/capric triglycerides, for example Miglyol™ 812 of Huls; caprylic/capric mono- and diglycerides, for example Capmul™ MCM of Abitec; polyoxyethylene caprylic/capric glycerides such as polyoxyethylene (8) caprylic/capric mono- and diglycerides, for example Labrasol™ of Gattefossé; propylene glycol fatty acid esters, for example propylene glycol laurate; polyoxyethylene (35) castor oil, for example Cremophor™ EL of BASF; polyoxyethylene glyceryl trioleate, for example Tagat™ TO of Goldschmidt; lower alkyl esters of fatty acids, for example ethyl butyrate, ethyl caprylate and ethyl oleate; and water.

Gelatin capsules

[0057] Any pharmaceutically acceptable gelatin capsules can be used to prepare a dosage form of the present invention, including hard and soft gelatin capsules. Such capsules can be prepared according to any suitable process.

Hard gelatin capsules

[0058] Non-limiting methods for preparing hard gelatin capsules are described in the following patents and/or publications, each of which is hereby incorporated by reference herein.

[0059] U.S. Patent No. 3,656,997 to Cordes.

[0060] U.S. Patent No. 4,231,211 to Strampfer *et al.*

[0061] U.S. Patent No. 4,263,251 to Voegle.

[0062] U.S. Patent No. 4,403,461 to Goutard *et al.*

[0063] U.S. Patent No. 4,705,658 to Lukas.

[0064] U.S. Patent No. 4,720,924 to Hradecky *et al.*

[0065] U.S. Patent No. 4,756,902 to Harvey *et al.*

[0066] U.S. Patent No. 4,884,602 to Yamamoto *et al.*

[0067] U.S. Patent No. 4,892,766 to Jones.

[0068] U.S. Patent No. 6,350,468 to Sanso.

[0069] International Patent Publication No. WO 84/00919 to Mackie.

[0070] International Patent Publication No. WO 85/04100 to Kalidindi.

ii. Soft gelatin capsules

[0071] In a preferred embodiment, capsule shells are soft gelatin capsule shells. Such shells can be prepared according to any suitable process including but not limited to the plate process, vacuum process, or the rotary die process. See, for example, (1) Ansel *et al.* (1995) in Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th ed., Williams & Wilkins, Baltimore, MD, pp. 176-182; and (2) Remington: The Science and Practice of Pharmacy, 19th Ed., Mack Publishing Co. Easton. PA, pp. 1646 - 1647, the above-recited pages of which are hereby incorporated by reference herein.

[0072] Non-limiting examples of suitable methods for preparing soft gelatin capsules are described in the following patents and publications, each of which is hereby incorporated by reference herein.

[0073] U.S. Patent No. 3,592,945 to Pesch.

[0074] U.S. Patent No. 4,609,403 to Wittwer *et al.*

[0075] U.S. Patent No. 4,744,988 to Brox.

[0076] U.S. Patent No. 4,804,542 to Fischer *et al.*

[0077] U.S. Patent No. 5,146,758 to Herman.

[0078] U.S. Patent No. 5,254,294 to Wunderlich *et al.*

[0079] U.S. S Patent No. 6,260,332 to Takayanagi.

[0080] U.S. Patent No. 6,238,616 to Ishikawa *et al.* and

[0081] International Patent Publication No. WO 92/15828 to Herman.

[0082] As used herein, unless specific context instructs otherwise, the term "capsule shell" (and "gelatin capsule shell") embraces capsule half-shells (that can cooperate to form a whole capsule shell) and whole capsule shells (that define a fill

volume). Such term also embraces soft gelatin capsule shells and hard gelatin capsules, irrespective of the process by which such shells are made.

[0083] The terms "sealed capsule shell", "sealed in a capsule shell", "sealing in the capsule shell" and the like are meant to denote a whole capsule shell that defines a fill volume, that such fill volume can contain a fill material, that such fill material is enclosed in the whole capsule shell, and that such enclosure affords the fill material more than a de minimis amount of protection from the atmosphere outside of the whole capsule shell.

Utility

[0084] Dosage forms of the invention are useful in treatment and prevention of a very wide range of disorders mediated by COX-2, including but not restricted to disorders characterized by inflammation, pain and/or fever. Such dosage forms are especially useful as anti-inflammatory agents, such as in treatment of arthritis, with the additional benefit of having significantly less harmful side effects than compositions of conventional NSAIDs that lack selectivity for COX-2 over COX-1. In particular, dosage forms of the invention have reduced potential for gastrointestinal toxicity and gastrointestinal irritation, including upper gastrointestinal ulceration and bleeding, by comparison with compositions of conventional NSAIDs. Thus dosage forms of the invention are particularly useful as an alternative to conventional NSAIDs where such NSAIDs are contraindicated, for example in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; gastrointestinal bleeding, coagulation disorders including anemia such as hypoprothrombinemia, hemophilia or other bleeding problems; kidney disease; or in patients prior to surgery or patients taking anticoagulants.

[0085] Contemplated dosage forms are useful to treat a variety of arthritic disorders, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis.

[0086] Such dosage forms are useful in treatment of asthma, bronchitis, menstrual cramps, preterm labor, tendonitis, bursitis, allergic neuritis, cytomegalovirus infection, apoptosis including HIV-induced apoptosis, lumbago, liver disease including hepatitis, skin-related conditions such as psoriasis, eczema, acne, burns, dermatitis and ultraviolet radiation damage including sunburn, and post-operative inflammation including that following ophthalmic surgery such as cataract surgery or refractive surgery.

[0087] Such dosage forms are useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis.

[0088] Such dosage forms are useful in treating inflammation in such diseases as migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, nephritis, hypersensitivity, swelling occurring after injury including brain edema, myocardial ischemia, and the like.

[0089] Such dosage forms are useful in treatment of ophthalmic disorders, including without limitation inflammatory disorders such as endophthalmitis, episcleritis, retinitis, iriditis, cyclitis, choroiditis, keratitis, conjunctivitis and blepharitis, inflammatory disorders of more than one part of the eye, *e.g.*, retinochoroiditis, iridocyclitis, iridocyclochoroiditis (also known as uveitis), keratoconjunctivitis, blepharoconjunctivitis, *etc.*; other COX-2 mediated retinopathies including diabetic retinopathy; ocular photophobia; acute trauma of any tissue of the eye including postsurgical trauma, *e.g.*, following cataract or corneal transplant surgery; postsurgical ocular inflammation; intraoperative miosis; corneal graft rejection; ocular, for example retinal, neovascularization including that following injury or infection; macular degeneration; cystoid macular edema; retrolental fibroplasia; neovascular glaucoma; and ocular pain.

[0090] Such dosage forms are useful in treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis, and in bone resorption such as that associated with osteoporosis.

[0091] Such dosage forms are useful for treatment of certain central nervous system disorders, such as cortical dementias including Alzheimer's disease, neurodegeneration, and central nervous system damage resulting from stroke, ischemia and trauma. The term "treatment" in the present context includes partial or total inhibition of dementias, including Alzheimer's disease, vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia and senile dementia.

[0092] Such dosage forms are useful in treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome and liver disease.

[0093] Such dosage forms are useful in treatment of pain, including but not limited to postoperative pain, dental pain, muscular pain, and pain resulting from cancer. For example, such dosage forms are useful for relief of pain, fever and inflammation in a variety of conditions including rheumatic fever, influenza and other viral infections including common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, and trauma following surgical and dental procedures.

[0094] Such dosage forms are useful for treating and preventing inflammation-related cardiovascular disorders, including vascular diseases, coronary artery disease, aneurysm, vascular rejection, arteriosclerosis, atherosclerosis including cardiac transplant atherosclerosis, myocardial infarction, embolism, stroke, thrombosis including venous thrombosis, angina including unstable angina, coronary plaque inflammation, bacterial-induced inflammation including Chlamydia-induced inflammation, viral induced inflammation, and inflammation associated with surgical procedures such as vascular grafting including coronary artery bypass surgery, revascularization procedures including angioplasty, stent placement, endarterectomy, or other invasive procedures involving arteries, veins and capillaries.

[0095] Such dosage forms are useful in treatment of angiogenesis-related disorders in a subject, for example to inhibit tumor angiogenesis. Such dosage forms are useful in treatment of neoplasia, including metastasis; ophthalmological conditions such as corneal graft rejection, ocular neovascularization, retinal neovascularization including neovascularization following injury or infection, diabetic retinopathy, macular degeneration, retrolental fibroplasia and neovascular glaucoma; ulcerative diseases such as gastric ulcer; pathological, but non-malignant, conditions such as hemangiomas, including infantile hemaginomas, angiofibroma of the nasopharynx and avascular necrosis of bone; and disorders of the female reproductive system such as endometriosis.

[0096] Such dosage forms are useful in prevention and treatment of benign and malignant tumors and neoplasia including cancer, such as colorectal cancer, brain cancer, bone cancer, epithelial cell-derived neoplasia (epithelial carcinoma) such as basal cell carcinoma, adenocarcinoma, gastrointestinal cancer such as lip cancer, mouth cancer, esophageal cancer, small bowel cancer, stomach cancer, colon cancer, liver cancer,

bladder cancer, pancreas cancer, ovary cancer, cervical cancer, lung cancer, breast cancer, skin cancer such as squamous cell and basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that effect epithelial cells throughout the body. Neoplasias for which dosage forms of the invention are contemplated to be particularly useful are gastrointestinal cancer, Barrett's esophagus, liver cancer, bladder cancer, pancreatic cancer, ovarian cancer, prostate cancer, cervical cancer, lung cancer, breast cancer and skin cancer. Such dosage forms can also be used to treat fibrosis that occurs with radiation therapy. Such dosage forms can be used to treat subjects having adenomatous polyps, including those with familial adenomatous polyposis (FAP). Additionally, such dosage forms can be used to prevent polyps from forming in subjects at risk of FAP.

[0097] Such dosage forms inhibit prostanoid-induced smooth muscle contraction by inhibiting synthesis of contractile prostanoids and hence can be of use in treatment of dysmenorrhea, premature labor, asthma and eosinophil-related disorders. They also can be of use for decreasing bone loss particularly in postmenopausal women (*i.e.*, treatment of osteoporosis), and for treatment of glaucoma.

[0098] Preferred uses for dosage forms of the invention are for treatment of rheumatoid arthritis and osteoarthritis, for pain management generally (particularly post-oral surgery pain, post-general surgery pain, post-orthopedic surgery pain, and acute flares of osteoarthritis), for treatment of Alzheimer's disease, and for colon cancer chemoprevention.

[0099] Besides being useful for human treatment, dosage forms of the invention are useful for veterinary treatment of companion animals, exotic animals, farm animals, and the like, particularly mammals. More particularly, dosage forms of the invention are useful for treatment of COX-2 mediated disorders in horses, dogs and cats.

EXAMPLES

[0100] The following non-limiting examples are provided for illustrative purposes only and are not to be construed as limitations.

Example 1

[0101] Three fill formulations, F1 - F3, were prepared as shown in Table 1. One ml of each fill formulation were filled into each of several standard (no primary or

secondary amine) soft gelatin capsules (R.P. Scherer).

Table 1. Composition of fill formulations F1 - F3

Component	F1	F2	F3
Celecoxib	200	278	270
PEG400	271	337	334
Tween80	217	195	194
Oleic Acid	61	80	78
PVP	47	-	-
Ethanol	113	-	-
Hydroxypropyl methylcellulose ("HPMC")	38	74	74
Water	26	-	10
Propyl gallate	1	2	2
Tromethamine	26	-	5
Dimethylamino-ethanol ("DMAE")	-	34	33
Total	1000	1000	1000

[0102] Filled capsules were placed in a sealed container and stored at 40 °C and 75% relative humidity for a period of up to 24 weeks. At various times during storage, capsules were removed from the closed container and evaluated, by visual inspection, for presence or absence of pellicle formation (*i.e.* cross-linking). Each evaluated capsule was assigned a numerical indicator based on any pellicle observed according to the following scale: (1) = no pellicle; (2) = thin, incomplete pellicle; (3) = thin, complete pellicle; (4) = strong, complete pellicle which inhibits compression of capsule; and (5) thick, strong, and severe pellicle. Pellicle formation observations are shown in Table 2.

Table 2. Pellicle formation after storage for up to 24 weeks at 40 °C and 75% relative humidity

Time (weeks)	F1	F2	F3
0	1	1	1
2		3	1
4	1	3	2
6		3	3
8	1	4	3
12	1	-	-
24	1	-	-

[0103] As shown in Table 2, capsules containing Fill Formulation F1 (comprising

tromethamine in an amount of about 3% by weight of the fill material) exhibited no pellicle formation during storage for a period of six months. By contrast, capsules containing Fill Formulation F2 (no primary or secondary amine compound) or F3 (0.5% tromethamine) exhibited pellicle formation by two and four weeks of storage, respectively.

Example 2

[0104] A test material comprising PEG 400 and 414 µg/ml formaldehyde was prepared. Four aliquots, A1 - A4, of the test material were drawn and placed in separate vials. Individually, one component selected from glycine, tromethamine, ethanolamine (or no additional component) was added to each vial in an amount of 5 mg/ml, as shown in Table 3, to form test samples A1 - A4, respectively.

Table 3. Composition of Test Samples A1 - A4

Test Sample	A1	A2	A3	A4
Aliquot	A1	A2	A3	A4
Additional component	None	Tromethamine	Ethanolamine	Glycine

[0105] Each of the test samples were stored at room temperature for a period of three days. After three days of storage, formaldehyde concentration in each sample was measured using HPLC. Amount of formaldehyde present in each sample (% weight of original amount) is shown in Table 4.

Table 4. Amount of formaldehyde present in Test Samples A1 - A4 after storage

Test Sample	A1	A2	A3	A4
Formaldehyde content	100	19.6	17.8	61.9

[0106] These data show that the primary amines tromethamine and ethanolamine reduced formaldehyde levels upon storage to a greater extent than did glycine. Without being bound by theory, formaldehyde is believed to be a chemical which causes and/or promotes gelatin cross-linking.

Example 3.

[0107] The cross-linking behavior of two soft gelatin formulations was investigated over a 6 month period. As shown below (Table 5), Formulation 30 (the control lot) contains dimethylaminoethanol ("DMAE") and no sulfite. Formulation 19

(the test lot) was similar to the Formulation 30, except that Formulation 19 additionally comprises sodium metabisulfite in the fill material.

Table 5. Fill material of Formulations 30 and 19 (mg/g)

Component	Formulation 30	Formulation 19
celecoxib	278	270
PEG 400	337	335
Tween 80	195	195
oleic acid	80	78
HPMC	74	74
DMAE	34	35
propyl gallate	2	2
water	-	7
sodium metabisulfite	-	4

[0108] Both soft gelatin capsule formulations were placed into non-induction-sealed hydroxypropyl ethylene bottles and stored at either 25° C and 60% RH or 40° C and 75% RH. Using such bottles, RH inside the bottles readily equilibrates with the RH outside of the bottles (60% or 75%). Periodically, capsules were tested for degree of cross-linking of the soft gelatin samples as estimated by the drug release profile.

[0109] Formulation 30. The Tier I drug release results for control Formulation 30 at 25° C / 60% relative humidity ("RH") and 40° C / 75% RH are shown in Figures 1 and 2 and the Tier II drug release results for the same lot and conditions are shown in Figures 3 and 4. As early as 1 month of storage, there was a marked delay in the Tier I drug release profile at both temperature conditions. This delay increased with storage time. The Tier II drug release profile at 25° C / 60% RH and at 40° C / 75% RH shows a significant but markedly reduced delay in release profile.

[0110] Formulation 19. The Formulation 19 Tier I drug release results for the 25° C / 60% RH condition are shown in Figure 5. No change in the drug release profile is observed through 6 months, indicating that no cross-linking has occurred. Accordingly, the analogous Tier II test for this sample was not performed. Figure 6 displays the Tier I results for Formulation 19 at 40° C / 75% RH. No change in drug release profile is observed for most of the stability time points with the exception of the 6 month time point. To determine if the change in drug release profile at 6 months is a result of cross-linking, the Tier II test was performed on this sample. The Tier II results are displayed in Figure 7. The Tier I and Tier II results are very similar for this 6 month sample indicating

that the change in drug release profile is not attributable to cross-linking.

[0111] These data indicate that there was severe cross-linking observed in the Formulation 30. The change in the Tier II drug release profile (i.e. reduced delay) indicates that Tier I delayed release is the result of cross-linking for this formulation and further indicates that a significant delay in the drug release profile in humans would be likely. The Formulation 19, containing sodium metabisulfite, exhibits no measurable cross-linking through 6 months at stringent (40° C / 75% RH) storage conditions. These data demonstrate that the addition of sodium metabisulfite to this formulation significantly reduces the rate of cross-linking and indeed may inhibit cross-linking completely. Without being bound by theory, sodium metabisulfite is believed to inhibit cross-linking by a process in which sodium metabisulfite reacts with aldehydes forming a bisulfite addition product. Thus, sodium metabisulfite can effectively scavenges aldehydes making them unavailable to promote cross-linking in the gelatin.

Example 4.

[0112] Four soft gelatin Celecoxib formulations were prepared as shown in Table 6 and tested for pellicle formation at 40°C and 75% relative humidity ("RH").

[0113] In absence of sulfite, complete pellicle formation was apparent after only 2 weeks storage at 40°C / 75% RH (Formulation 30; cross-linking rating =3).

[0114] At a Tris concentration of 5 mg/g in the formulation (Formulation 20), delayed pellicle formation but was insufficient to prevent a complete pellicle formation (the cross-linking rating =3) upon 1.5 months storage under 40°C / 75% RH.

[0115] At a higher Tris concentration in the formulation (26 mg/g, Formulation 50), gelatin cross-linking is completely prevented upon 6 months storage under 40°C / 75% RH.

[0116] A low sodium metabisulfite (SMB) concentration of 4 mg/g in the formulation (Formulation 19) appeared sufficient to prevent the pellicle formation upon 2 months storage under 40°C / 75% RH.

Table 6. Gelatin cross-linking analysis of soft gelatin at 40°C/75% RH storage

Months at 40°C/ 75% RH	Formulation 50 mg/ml	Formulation 30 mg/ml	Formulation 19 mg/ml	Formulation 20 mg/ml
	Celecoxib 200 PEG400 271 Tween80 217 Oleic acid 61 PVP 47 EtOH 113 HPMC 38 propyl gallate 1 water 26 **Tris 26**	Celecoxib 278 PEG400 337 Tween80 195 Oleic acid 80 HPMC 74 DMAE 34 propyl gallate 2	Celecoxib 270 PEG400 335 Tween80 195 Oleic acid 78 HPMC 74 DMAE 35 propyl gallate 2 water 7 **SMB 4**	Celecoxib 270 PEG400 334 Tween80 194 Oleic acid 78 HPMC 74 DMAE 33 propyl gallate 2 water 10 **Tris 5**
0	**1**	**1**	**1**	**1**
0.5		**3**	**1**	**1**
1	**1**	**3**	**1**	**2**
1.5		**3**	**1**	**3**
2	**1**	**4**	**1**	**3**
3	**1**			
6	**1**			

Example 5.

[0100] In order to gain insight in to the mechanism by which Tris (hydroxymethyl aminomethane) in fill material of a gelatin capsule prevents pellicle formation, a dosage form (of Formulation X-60 set forth in Table 7) was prepared and stored under two different conditions as shown in Table 8. At the times indicated, capsules were removed and Tris content was quantified in the fill material and in the capsule. As shown in Table 8, upon storage with time, Tris content in the capsules increased and Tris content in the fill material decreased in comparison to the initial formulation.

Table 7. Soft gelatin capsule Formulation X-60

Ingredient	Formulation X-60
Celecoxib	200
PEG 400	271
Tween 80	217
Oleic acid	61
Tris	26
Water	26
Propyl gallate	1
PVP-12PF	47
Abs. EtOH	113
HPMC-E5	38
Total	1000 mg/g
Fill Volume (200 mg drug)	0.92 mL
Dosage Form	18 Oblong soft gelatin capsule

Table 8. Tris content in capsule shells following storage of Formulation X-60

Soft gelatin capsule Storage conditions	Tris in fill (mg)	Tris in shell (mg)
25°C/60% RH		
T=2 months	18.7	5.3
T=6 moths	17.9	6.0
T=8 months	16.4	6.5
T=10 months	17.6	7.0
40°C/75% RH		
T=2 months	13.5	10.5
T=6 moths	10.8	11.1
T=8 months	10.0	10.6
T=10 months	10.0	13.3
26 mg Tris in a soft gelatin capsule at T=0		